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SUMMARY OF TOXICOLOGY DATA ON DAMINOZIDE AND UDMH

Review of "Old" Data by EPA and the FIFRA SAP

On September 26, 1985 the FIFRA Scientific Advisory Panel reviewed the then-existing data on daminozide and UDMH to determine the impact of those chemicals on health and the environment. The FIFRA SAP reviewed five studies: Haun 1984, NCI 1978, Toth 1977a, Toth 1977b, and Toth 1973. EPA summarized the FIFRA SAP's recommendation and the Agency's resulting position: "Each of these studies, however, has been examined by the Agency and the FIFRA Scientific Advisory Panel (SAP), and has been found not to provide an adequate basis for regulatory action at this time." 52 Fed. Reg. 1913 (Jan. 16, 1987) (see Appendix 5). EPA subsequently stated that "audits and reviews of these studies have revealed that some of the studies yielded equivocal results and that the other studies have serious flaws or shortcomings in the test methodology and documentation. These facts have led EPA to conclude that the existing studies, singly or in combination, are inadequate to serve as the basis for regulatory action against daminozide under the Federal Insecticide, Fungicide and Rodenticide Act." 52 Fed. Reg. 28257. (July 29, 1987) (see Appendix 6). EPA explained:

> After its review of the studies and critiques, the SAP concluded that, while some of the studies (those performed by Toth, et al.) "give rise to concern about the possible oncogenicity of daminozide," the data are inadequate to allow a qualitative risk assessment of the oncogenic potential of daminozide, i.e., an assessment of how likely it is that daminozide in fact increases the incidence of cancer. The SAP also found that the data are inadequate to allow a quantitative risk assessment.
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> With respect to UDMH, the SAP found that a recent inhalation study (conducted by Haun, et al.) provides some evidence of potential oncogenicity, but that discrepancies in the study require further clarification. The SAP found use of these data to evaluate dietary risk to be questionable. (A subsequent EPA audit of the inhalation study concluded that it is unusable for regulatory purposes because the source and chemical composition of the test substance could not be determined from the underlying records of the study and because the boiling point of the chemical that was used as the test substance was reported to be some 40 degrees Centigrade higher than that of UDMH.)

52 Fed. Reg. 28257 (Appendix 6). Thus, according to EPA and the FIFRA SAP, the previously existing data do not constitute scientifically valid testing according to generally accepted principles and do not show that daminozide or UDMH is carcinogenic.

Dr. Christopher Wilkinson also has conducted a review of the prior studies. Dr. Wilkinson agrees that:

> The results of the older data base provide no compelling evidence that either daminozide or UDMH can be considered rodent carcinogens even at relatively high concentrations. Unfortunately, the data base is notable for its uniformly poor quality and, as pointed out by the EPA's SAP, it is not sufficient for either a qualitative or quantitative

evaluation of oncogenic potential. Base on current GLP requirements and cancer risk assessment guidelines, most of the data would be unacceptable. (See Appendix 2).

Mutagenicity Studies

Daminozide was previously shown to be non-mutagenic in a battery of five studies which included an Ames, E. coli DNA damage, S. cerevisiae genetic damage, mouse lymphoma and mouse dominant lethal assay. EPA requested four additional mutagenicity studies on UDMH. EPA reviewed and accepted as negative three of these studies. These studies are an Ames, CHO chromosome aberration assay and a DNA repair (UDS) assay. A fourth study, a CHO/HPRT gene mutation assay, which originally gave an equivocal result, was repeated and was negative. These data support the conclusion that daminozide and UDMH are non-mutagenic.

Review of New Oncogenicity Studies

Daminozide

Daminozide oncogenicity studies in the rat and mouse were reported by IRDC in August 1988. Daminozide was administered in the diet of Charles River CD-1 mice at dosage levels of 300, 3,000, 6,000 and 10,000 ppm, and in Fischer 344 rats at dosage levels of 100, 500, 5,000 and 10,000 ppm. The text of these reports is given in Appendix 3 and 4. Both reports concluded

that there were no oncogenic effects related to administration of daminozide.

In the daminozide mouse study there was a slight increase in the incidence of pulmonary neoplasms in treated animals and in the incidence of hemangiosarcomas of the liver in male mice. However, these effects were not considered by IRDC to be biologically significant.

The review of the daminozide oncogenicity studies by Dr. Christine Chaisson (Appendix 1) confirms IRDC's conclusion that these studies do not show that daminozide causes cancer. Dr. Chaisson concluded that "with the absence of genotoxic activity and no significant carcinogenic observations, the weight of the evidence clearly favors classification of daminozide as Non-Carcinogenic."

UDMH

UDMH oncogenicity studies conducted by IRDC in the rat and mouse are scheduled to be reported in September 1989. In addition, a very high dose mouse study is scheduled to be reported in January 1990. The schedule for the UDMH studies is presented in the table below:

SCHEDULE FOR UDMH ONCOGENICITY STUDIES

Animal Species	Date Started	Report Dates	Interim Results At
Rat	1/87	9/89	1 year

Mouse	1/87	9/89	8 months, 1 year
Mouse (very high doses)	5/87	1/90	8 months, 1 year

Because final results from the UDMH oncogenicity studies are not available, Uniroyal believes that it would be appropriate to reserve decision on UDMH until those results are received and can be evaluated.

Interim results after one year in the UDMH rat and mouse oncogenicity studies indicate no oncogenic effects. (See Appendix 7 and 8). UDMH was administered in water to the rat at dosage levels of 1, 50 and 100 ppm, and to the mouse at dosage levels of 1, 5 and 10 ppm in males and 1, 5 and 20 ppm in females.

In the high dose UDMH mouse oncogenicity study (Appendix 9) where UDMH was administered in water at dosage levels of 40 and 80 ppm, an increase in lung adenomas was found in the high dose treated animals (80 ppm group) as compared to controls at the 8 month interim sacrifice. However, this finding was accompanied by significant liver and blood effects which suggest that the Maximum Tolerated Dose (MTD) was exceeded. A one year interim sacrifice was recently completed. Results show an increase in benign lung tumors in treated vs. control animals. Blood vessel tumors were also increased in the 80 ppm treated groups. Again, significant toxicity was found in the treated animals which was

accompanied by a marked increase in mortality in the 80 ppm dosage groups vs. control groups. UDMH produced non-neoplastic toxicity to the liver in mid and high dose males and to a lesser degree in females. This hepatotoxicity consisted of accumulation of brown pigment, hypertrophy, single cell necrosis, telangiectasis and hyperplasia of endothelial cells. Biochemical tests were also indicative of liver toxicity, where alanine aminotransferase and sorbitol dehydrogenase levels were significantly elevated in both males and females at 40 and 80 ppm. In addition, males at both 40 and 80 ppm had statistically significant decreases in mean erythrocytes, hemoglobin and hematocrit values at 12 months.

The study also reported an increase in mortality in the 80 ppm dosage group and this was considered a treatment related effect. Survival is summarized in the table below through week 81 of the study.

% SURVIVAL UDMH MOUSE STUDY (High Dose)

Week of Study	0		40		80	
M F	M	F	M	F		
52	90	92	90	86	74	78
71	80	84	80	70	42	48
77	76	76	76	62	30	40
81	74	68	68	58	18	30

It is evident from the decreased survival, and the liver and blood toxicity observed, that the MTD has been exceeded in this study. A proper evaluation of the carcinogenic potential

of UDMH most await the results of the UDMH rat and mouse studies which are being conducted at dosage levels that more closely approximate an MTD.

The interim results from the UDMH studies have been reviewed by Dr. Chaisson. (Appendix 1). Her report states:

> Based on preliminary data, the worst-case evaluation would be that UDMH has shown carcinogenic effects in mice when fed overtly toxic levels. The genotoxicity data are negative and do not support the carcinogenicity of UDMH. The preliminary data from the rat studies are negative and do not support the observations in the high-dose mice. The low-dose mouse study, conducted at does which do not compromise the viability of the test animal or drastically alter the basic physiological integrity of the animals, also contradicts the high-dose observations.
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> The evidence, therefore, suggests that UDMH is not directly expressing carcinogenic potential.

Conclusion

Both the United States Environmental Protection Agency and the FIFRA Scientific Advisory Panel concluded that previously-existing data on daminozide and UDMH were inadequate to classify those chemicals as carcinogens.

The final results of new oncogenicity studies on daminozide in the rat and the mouse do not indicate that daminozide is a carcinogen.

One-year interim results indicate no oncogenic effects in the UDNH rat and mouse studies, and positive interim results in the high dose mouse study are accompanied by indications that the MTD had been exceeded. Evaluation of UDMH should be reserved until the final results of the ongoing studies are available.